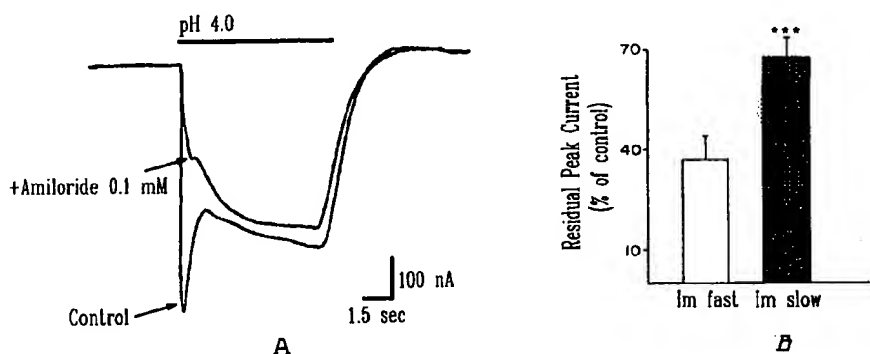




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(54) Title: DNA ENCODING A HUMAN PROTON-GATED ION CHANNEL AND USES THEREOF



## (57) Abstract

Small changes of extracellular pH activate depolarizing inward currents in most nociceptive neurons. It has been recently proposed that acid sensitivity of sensory as well as central neurons is mediated by a family of proton-gated cation channels structurally related to C. elegans degenerins and mammalian epithelial sodium channels. We describe here the molecular cloning of a novel human proton receptor, hASIC3, a 531 amino acid-long subunit homologous to rat DRASIC. Expression of homomeric hASIC3 channels in *Xenopus* oocytes generated biphasic inward currents elicited at pH < 5, providing the first functional evidence of a human proton-gated ion channel. Contrary to the DRASIC current phenotype, the fast desensitizing early component and the slow sustained late component differed both by their cationic selectivity and by their response to the antagonist amiloride, but not by their pH sensitivity (pH<sub>50</sub> = 3.66 vs 3.82). Using RT-PCR and mRNA blot hybridization, we detected hASIC3 mRNA in sensory ganglia, brain and many internal tissues including lung and testis, so hASIC3 gene expression was not restricted to peripheral sensory neurons. These functional and anatomical data strongly suggest that hASIC3 plays a major role in persistent proton-induced currents occurring in physiological and pathological conditions of pH changes, likely through a tissue-specific heteropolymerization with other members of the proton-gated channel family.